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**Pharmacological induction of pancreatic islet cell transdifferentiation: relevance to type I diabetes.**

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**Public Summary:**

Type I diabetes (T1D) is an autoimmune disease in which an immune response to pancreatic beta-cells results in their loss over time. Although the conventional view is that this loss is due to autoimmune destruction, we present evidence of an additional phenomenon in which autoimmunity promotes islet endocrine cell transdifferentiation. The end result is a large excess of delta-cells, resulting from alpha- to beta- to delta-cell transdifferentiation. Intermediates in the process of transdifferentiation were present in murine and human T1D. Here, we report that the peptide caerulein was sufficient in the context of severe beta-cell deficiency to induce efficient induction of alpha- to beta- to delta-cell transdifferentiation in a manner very similar to what occurred in T1D. This was demonstrated by genetic lineage tracing and time course analysis. Islet transdifferentiation proceeded in an islet autonomous manner, indicating the existence of a sensing mechanism that controls the transdifferentiation process within each islet. The finding of evidence for islet cell transdifferentiation in rodent and human T1D and its induction by a single peptide in a model of T1D has important implications for the development of beta-cell regeneration therapies for diabetes.

**Scientific Abstract:**

Type I diabetes (T1D) is an autoimmune disease in which an immune response to pancreatic beta-cells results in their loss over time. Although the conventional view is that this loss is due to autoimmune destruction, we present evidence of an additional phenomenon in which autoimmunity promotes islet endocrine cell transdifferentiation. The end result is a large excess of delta-cells, resulting from alpha- to beta- to delta-cell transdifferentiation. Intermediates in the process of transdifferentiation were present in murine and human T1D. Here, we report that the peptide caerulein was sufficient in the context of severe beta-cell deficiency to induce efficient induction of alpha- to beta- to delta-cell transdifferentiation in a manner very similar to what occurred in T1D. This was demonstrated by genetic lineage tracing and time course analysis. Islet transdifferentiation proceeded in an islet autonomous manner, indicating the existence of a sensing mechanism that controls the transdifferentiation process within each islet. The finding of evidence for islet cell transdifferentiation in rodent and human T1D and its induction by a single peptide in a model of T1D has important implications for the development of beta-cell regeneration therapies for diabetes.

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